Please amend the specification in Figure 1B (sheet 1/8) as follows:

$RS(H)_6RS$ (SEQ ID NO:47)

$RS(H)_6RS(H)_6RS$ (SEQ ID NO:48)

RSARPRSASGPRSPMHTSTTPPRS (SEQ ID NO:49)

RSRTHGPEGRPRS (SEQ ID NO:50)

RSSLSLFFRNRRSSVEDAHQTMRS (SEQ ID NO:51)

RSGANGRELHTRS (SEQ ID NO:52)

RSFSETAQSTGRSYVKFVWRHHRS (SEQ ID NO:53)

RSARGHVLISERS (SEQ ID NO:54)

RSHLSRLRGNRRS (SEQ ID NO:55)

RSRGVNDSPNGRSITHIRRTHKRS (SEQ ID NO:56)

RSQVLRRPELIRSMPEHRRREHRS (SEQ ID NO:57)

RSERRTGETGLRSHYGQLGYRRRS (SEQ ID NO:58)

RSLRNGILSRHRS (SEQ ID NO:59)

RSTVNGCVSHSRSGGLRASREVRS (SEQ ID NO:60)

RSKVRLRDEHERS (SEQ ID NO:61)

RSEGRHRRGGMRS (SEQ ID NO:62)

(RX_2RS) (SEQ ID NO:64)

(PXRS) (SEQ ID NO:65)

$(TX_4HXKDRS)$ (SEQ ID NO:63)

In accordance with 37 C.F.R. § 1.121(b)(iii), Applicants submit a version of the amended specification in Appendix A, marked up to show all the changes relative to the previous version of the specification.

Rejections under 35 U.S.C. § 112

The Office Action rejects claims 1-15 and 18-25 under 35 U.S.C. § 112, second paragraph, as allegedly being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In particular, the Office Action states that the use of the language "first kind" and "second kind" is vague and indefinite.

Applicants respectfully disagree that the terminology "first kind" and "second kind" is vague or indefinite. The terms are used in accordance with their customary dictionary definitions. Further, the specification uses and describes these terms consistently and thoroughly. These terms are used merely to distinguish between two types of domains and not indicate any type of sequential order. In the recombinant cell, as recited in the claims, both kind of domains are present and "first kind" and "second kind" are utilized to describe the product with descriptive features, but not with reference to a process by which the recombinant cell is made. Applicants respectfully request that the rejections of claims 1-15 and 18-25 under 35 U.S.C. § 112, second paragraph, be removed and that the claims be found to be in a condition for allowance.

Rejections under 35 U.S.C. § 103(a)

Sousa et al.

The Office Action states that claims 1, 2, 12, 13, 15, and 18 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Sousa et al., "Enhanced metalloadsorption of bacterial cells displaying poly-His peptides", *Nature Biotechnology*, Volume 14, pp. 1017-1020 (August 1996) ("Sousa et al."). As basis for these rejections, the Office Action states:

> Sousa et al. suggest the use of "flagellar proteins of Gram-negative bacteria as anchor sites for peptides" (p. 1017, 1st column, 1st paragraph). The reference further points to the examination of designing these proteins with metal-binding properties with the use of "one or two histidine (His) clusters" (p. 1017, 1st column, 2nd paragraph) with peptides of various lengths upon Escherichia coli cells; adhesion to a Ni compound is suggested on page 1019 (1st column, 2nd paragraph) as seen in claim 10, line 3. The enrichment of the cell population containing these Ni compound binding heterologous proteins is suggested by the use of their adhesion to beads described on page 1019 (2nd column, 4th paragraph). Although, Sousa et al. practices the method upon a LamB protein, the claimed FimH protein is also a cell surface fibril; thus Sousa et al. motivates the recombinant cells of claims 1, 2, 12, 13, 15, and 18.

Applicants respectfully submit that Sousa et al. not suggest any specific flagellar proteins. Further, Sousa et al. not suggest the modification of adhesins to obtain heterobinary adhesin proteins with two different functional binding sites. In contrast to the present invention, the actual work disclosed by Sousa et al. is the modification of LamB protein to incorporate therein a metal binding poly-His tag.

As is well known in the art, LamB is not a fimbrial protein, but instead is an outer membrane protein. LamB is, to a large extent, buried in the outer membrane of the bacterial cell and not located at the fimbriae. As is known in the art, adhesins are generally defined as molecules expressed on the surface of a cell, mediating the adhesion of the cell to other cells or to an extracellular matrix. In contrast, LamB is not an adhesins. Instead, LamB acts as a maltoporin protein (i.e., creating a pore entry in the cell for maltodextrine, maltose and some other monosaccharides). The LamB protein also acts as a receptor for phage lambda (hence its name, LamB).

By teaching and disclosing the use of LamB, Sousa et al. explicitly teach away from the adhesins of the present invention. Further, Sousa et al. do not disclose nor suggest any specific flagellar proteins, much less suggest the modification of adhesins to obtain heterobinary adhesin proteins with two different functional binding sites such as claimed in the present invention.

Absent these disclosures, suggestions or teachings, one of ordinary skill in the art would not be prompted to arrive at the present invention in view of Sousa et al.

For at least the foregoing reasons, claims 1, 2, 12, 13, 15, and 18 are not obvious in view of Sousa et al. Applicants respectfully request that all rejections of claims 1, 2, 12, 13, 15, and 18 be removed and that the Examiner find the claims to be in a condition for allowance.

Sousa et al., in view of Pallesen et al. and Georgiou et al.

The Office Action states that claims 1-10, 12, 13, 15, and 18-25 are rejected under 35 U.S.C. § 103(a) as allegedly being unpatentable over Sousa et al. in view of Pallesen et al., "Chimeric FimH adhesin of type 1 fimbriae: a bacterial surface display system for heterologous sequences", Microbiology (1995), 141, 2839-2848 ("Pallesen et al.") and Georgiou et al., "Display of heterologous proteins on the surface of microorganisms: from the screening of combinatorial libraries to live recombinant vaccines", Nature Biotechnology, Volume 15, pp. 29-34 (January 1997) ("Georgiou et al."). As basis for these rejections, the Office Action states:

> Pallesen et al. describes a method of engineering a chimeric FimH adhesin by way of insertion into plasmids; for DNA segment for example that is "162 nucleotides encoding 52 [...] amino acids" (p. 2842, 2nd column, 2nd paragraph). A heterologous epitope on a FimH component is clearly displayed in Figure 2, page 2840. Georgiou et al. within the abstract, in view of Sousa et al. and Pallesen et al., clearly motivates the display of peptide libraries encoding heterologous proteins in bacteria, in particular E. coli, as recited in claims 18-25.

Pallesen et al. disclose modifications of FimH to display peptide sequences as antigens. The schematic drawing of Figure 2, on page 2840 of Pallesen et al., indicates the position of a heterologous epitope. However, the schematic drawing does not indicate whether the intrinsic binding domain is affected or not. Rather, Pallesen et al. report that foreign insert results in reduced adhesiveness (*see* p. 2846, 2nd col., lines 1-12).

Thus, Pallesen et al. does not direct the skilled person toward the present invention. The claims of the present invention comprise the making of binary adhesins with two co-exisiting binding sites--the original binding sites, which is optionally modified, and a non-naturally occurring binding site. In contrast, the disclosures of Pallesen et al. explicitly teach away from the making of binary adhesins with two co-existing binding sites. The teachings and disclosures of Pallesen et al., either by themselves or in combination with Sousa et al. and/or Georgiou et al. and/or any other reference, would not allow one of ordinary skill in the art to arrive at the claims of the present invention. As such, Applicants respectfully submit that the claims of the present invention are not obvious in view of Pallesen et al. by itself or in combination with any other reference(s).

Likewise, Applicants respectfully submit that the claims of the present invention are not obvious in view of Georgiou et al. In contrast to the present invention, Georgiou et al. do not indicate that it is possible to insert foreign peptide domains providing non-naturally occurring binding sites while maintaining the affinity of the intrinsic binding domain of a binding protein. Applicants respectfully submit that not many proteins will tolerate relatively large foreign inserts in their surface exposed domains and still retain their natural function. Therefore, the results underlying the present invention were in fact quite surprising. One of ordinary skill in the art would not have been inspired to arrive at this advantage and element of the present invention from the disclosures and teachings of Georgiou et al., either by itself or in combination with any other reference(s).

For at least the foregoing reasons, Applicants respectfully submit that claims 1-10, 12, 13, 15, and 18-25 are not obvious under 35 U.S.C. § 103(a). Applicants respectfully request that the rejections of the claims be removed and that they be found in a condition for allowance.